AF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/058,291	01/30/2002	James L. Hartley	0942.285000I/RWE/BJD	3302

26111 7590 10/21/2005

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,291	HARTLEY ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,36,38-54,58-66,69-75,77,79-88,90-93 and 95-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 28 July 2005, canceling claims 55-57, 89, 94, and amending claims 39-41, 43-45, 47, 52, 58-60, 62, 69, 72, 101, 104, 107 and 110. Claims 35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112 are currently pending and under consideration in this action.

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. As no new grounds of rejection are set forth that are not necessitated by material changes to the claims, **this action is made FINAL**.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

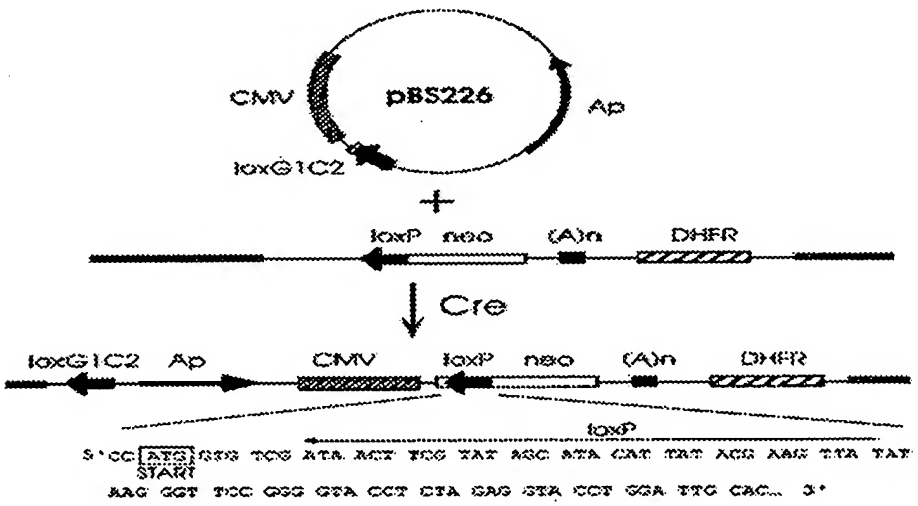
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. **Claims 35-36, 35-49, 69, 72, 75, 79-82, 97, 99, 101-102, 107-108 and 110-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukushige et al. (Proc. Natl. Acad. Sci. 1992; 89: 7905-9; hereinafter "Fukushige").**

This rejection is of record and repeated herein, with some modification so as to address amendments to the claims. A response to Applicant's arguments is set forth immediately following the body of this rejection.

The limitation "immediately adjacent" is interpreted to mean one structure is next to another structure (e.g., instant Drawings, 4C); the limitation is not interpreted to mean that there are not intervening sequences between depicted structures. In addition, the limitation "first" and "second portion" of an antibiotic resistance gene are interpreted as broadly as reasonable to include a promoter as representing a one portion and driving transcription of a an antibiotic gene (i.e., second portion).

Fukushige teaches nucleic acid molecules involved in site-specific recombination. More particularly, the nucleic acid molecule comprises a promoter immediately adjacent to a *lox*P site-specific recombination site, which is in turn next to a *neo* gene, as depicted in the figure below:



(See, p. 7906, Figure 2).

The expression vector comprises a CMV promoter and the antibiotic resistance gene *neo*. Furthermore, the reference teaches that an expression cassette/unit comprises two *lox* sites (Supra, schematic depicting *lox*G1C2 and *lox*P). In addition, the reference teaches that CHO cells are transfected with or contain the expression vector. (e.g., p. 7905, col. 2). Further, the nuclei acid molecule comprises multiple cloning sites. (e.g., p. 7906, Fig. 1A). In sum, the reference anticipates the rejected claims.

Response to Arguments

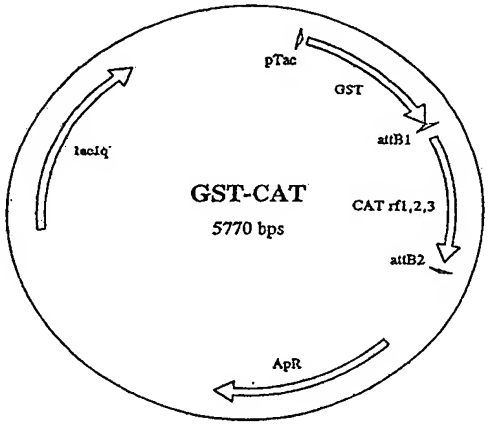
Applicant's arguments filed 07/28/2005 have been fully considered but they are not persuasive. Applicant asserts that Fukushige does not teach the limitation "immediately adjacent" as it applies to a promoter, an antibiotic resistance gene and a site-specific recombination site (i.e., *lox*P). More particularly, Applicant asserts that Fukushige teaches that there are intervening sequences between the preceding functional elements thus does not meet the limitation "immediately adjacent". (e.g., Remarks, pp. 27-28).

In addition, Applicant asserts that Fukushige is limited to *lox*P site-specific recombination sites, contrary to the instantly amended claims 52-54, 58-64, 87-88, 90-91 and 104-105. (Remarks, p. 28, bottom). In view of the amendments delimiting said claims to "lambdoid *att* site or a mutant thereof", the rejection is withdrawn. Thus, as to the rejected claims the only issue is whether Applicant's exclusive interpretation of the limitation "immediately adjacent" is correct.

Applicant suggests that the term "immediately adjacent" must be interpreted to mean that there are no intervening nucleotides between two structures. (e.g., Remarks, p. 25, middle).

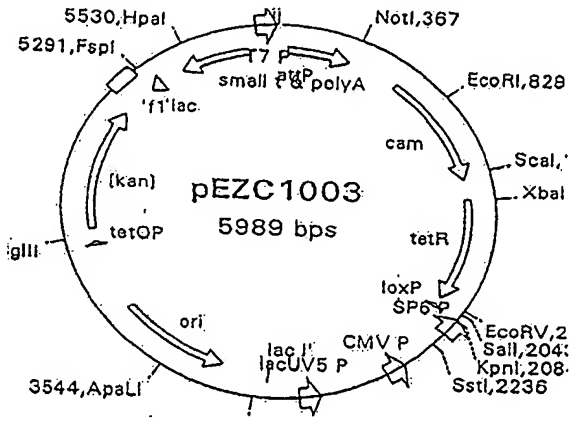
One of ordinary skill in the art will recognize that when read in the context of an expression vector a reasonable interpretation of the term "immediately adjacent" is that one functional element is *next to* another functional element. (e.g., Action, mailed 04/28/2005; p. 13). In other words, absent an exclusive definition for the term "immediately adjacent", the artisan would not interpret the term to mean that not a single nucleotide is present as between two functional elements on an expression vector/nucleic acid molecule.

However, as noted in the previous action, there is no such exclusive definition provided in the specification. Furthermore, the drawings on which Applicant relies cannot be reasonably interpreted to support such an exclusive definition. (e.g., Figures 4C, 8B, 8I and 8J). In fact, as an exemplary schematic, Fig. 8I teaches that either *att*B1 or *att*B2 are immediately adjacent to GST and CAT genes respectively:



In other words, in examining the preceding schematic one of ordinary skill in the art will recognize the absence of functional structures in between the site-specific recombination sites and a particular gene.

To further demonstrate that it is reasonable to interpret the limitation "immediately adjacent" to mean two functional structures that are present next to each other Figure 4C of the instant disclosure is reproduced below in salient part:



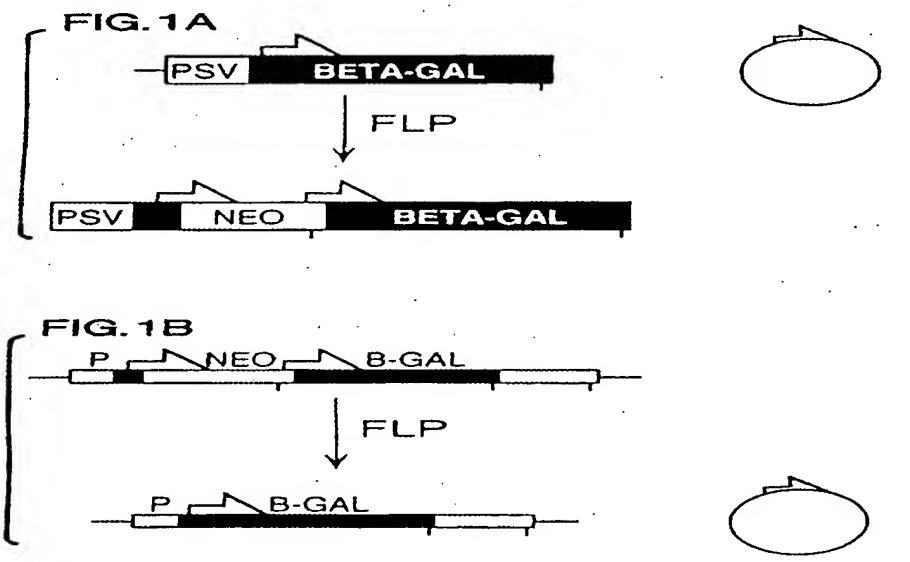
In examining the schematic there is no reason for interpreting the limitation "immediately adjacent" to mean that there is not a single nucleotide(s) between the claimed functional structures (e.g., CMV promoter and *lox*P site). Indeed, in observing the drawings, the claims and the disclosure on whole, and absent a definition to the contrary, the artisan would reasonably interpret the term "immediately adjacent" to mean two functional structures present next to each other without additional intervening functional structures. As such, Fukushige anticipates the rejected claims thus this rejection is maintained.

2. **Claims 39, 43, 47-49, 79, 81 and 101-102 are rejected under 35 U.S.C. 102(e) as being anticipated by Wahl et al. (US 5,677,177; hereinafter the '177 patent).**

This rejection is of record and repeated herein with modification to address amendments to the claims. A response to Applicant's arguments is set forth immediately following the body of this rejection. The claims are interpreted consonant with what is stated above.

The '177 patent teaches a site-specific recombination –mediated gene modification process. More particularly, the reference teaches nucleic acid molecules that contain a site-specific recombination site (i.e., FLP target sites). (e.g., col. 8, Example 1). Furthermore, the nucleic acid molecule has more than one of said recombination sites. (e.g., Fig. 2A; col. 8, l. 58). Further, the reference teaches that a promoter element is separated from an antibiotic resistance gene (i.e., NEO for neomycin) as is clearly depicted in the figure reproduced below:

U.S. Patent Oct. 14, 1997 Sheet 1 of 3 5,677,177



The schematic demonstrates that a promoter (i.e., *P* or *PSV*) is separated from an antibiotic resistance gene - NEO.

Further, the nucleic acid molecule comprises two site-specific recombination sites. (block arrows designating *FLP* sites). Furthermore, the nucleic acid molecules are vectors or expression vectors in that host cells transfected with said nucleic acid molecules are utilized to express proteins encoded on the nucleic acid vectors. (e.g., col. 9 to col. 10, Table 1; col. 11, Example 2; col. 12, Example 3). In addition, the vector comprises multiple cloning sites. (e.g., col. 9, ll. 10-15). Therefore, the '177 patent anticipates the rejected claims.

Response to Arguments

Applicant's arguments filed 07/28/2005 have been fully considered but they are not persuasive. Effectually, Applicant's arguments are based on the interpretation of the limitation "immediately adjacent" (Remarks, p. 25, top), as discussed in the preceding rejection. (Supra, Rejection No. 1, Response to Arguments). No other arguments are presented.

As discussed above, the limitation "immediately adjacent" is not interpreted to mean that as between to functional elements on an nucleic acid molecule/expression construct there can be an intervening nucleotide(s). The '177 patent teaches a nucleic acid molecule where a promoter and an antibiotic resistance gene are next to a site-specific recombination site. Thus for the reasons of record and stated hereinabove, the '177 anticipates the rejected claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 35-36, 38-51, 65-66, 69-75, 79-86, 92-93, 95-103 and 107-112, rejected under 35 U.S.C. 103(a) as being unpatentable over Fukushige et al. and Wahl et al. (US 5,677,177), and further in view of Lenski et al. (J. Bact. 1994; 176: 3140-47).

This rejection is of record and repeated herein. A response to Applicant's arguments is set forth immediately following the body of this rejection. The claims are interpreted consonant with what is stated above. In addition, the teachings of Fukushige and the '177 patent are incorporated and applied herein consonant with what is stated above.

Additional embodiments are directed to the antibiotic resistance gene as being chloramphenicol and the host cell as bacterial, i.e., *E. coli*.

Neither Fukushige or the '177 patent explicitly teach that chloramphenicol and *E. coli* can respectively be utilized as the antibiotic resistance gene or the host cell. However, the '177 patent teaches that genes that can be operably linked to site-specific recombination sites can be any selectable markers or genes for antibiotic resistance, relative to the phenotype of the host cells. (e.g., col. 6, ll. 37-47). In any event, utilizing bacterial host cells and selecting various selectable markers or antibiotic resistance genes entail nothing more than routine molecular

biology techniques. (e.g., mobilizing one gene to substitute another or transforming a bacterial host cell versus a eukaryotic host cell utilizing shuttle vectors).

Indeed, Lenski et al. teach several different antibiotic resistance genes that are utilized as selection markers in bacterial host cells. Further, Lenski et al. assay the various resistance genes, including chloramphenicol, and in the most widely studied and utilized bacterial host cell – *E. coli*. (e.g., pp. 3142-44; and entire document).

Therefore, it would have been obvious to use a host of different antibiotic genes, such as chloramphenicol in the nucleic acid molecules as taught by Fukushige or the '177 patent. One would have been motivated to utilize different selectable markers and in different host cells in which the selectable marker exhibits an observed phenotype change. Particularly, one would have been motivated to utilized chloramphenicol so as to extend the range of antibiotic resistance genes that can be utilized. Further, one would have been motivated to utilize *E. coli* as a host cell which as Lenski et al. teach effectively displays a phenotypic change utilizing chloramphenicol as a selective gene in phenotypic selection of a host cell comprising a target nucleic acid molecule such as those taught by Fukushige or the '177 patent. Given the level of skill at the time of invention and given that the modifications necessary would entail mere remedial molecular biology, there would have been a reasonable expectation of success to substitute chloramphenicol and utilize *E. coli* as a host cell in constructing nucleic acid molecules for site-specific recombination.

Response to Arguments

Applicant's arguments filed 07/28/2005 have been fully considered but they are not persuasive. The rejection is withdrawn with respect to claims 52-54, 58, 62-64, 87-88, 90 and

104-105. As to the remaining rejected claims, Applicant does not present any new arguments that have not been addressed above. More particularly, Applicant asserts that the Fukushige reference and the '177 patent are deficient as primary references because they fail to meet the limitation "immediately adjacent". Therefore, Applicant asserts that the primary references are deficient and the secondary reference (Lenski et al.) does not rectify said deficiency.

Whether the primary references are deficient once again turns on the interpretation of the limitation "immediately adjacent". Reiterating what is already stated above, the limitation "immediately adjacent" is not interpreted to mean that there cannot be any nucleotide(s) between the functional elements of the claimed nucleic acid molecules. (Supra, Rejection Nos. 1-2, under "Response to Argument"). Therefore, since the primary references teach promoter elements and antibiotic resistance genes that are *immediately adjacent* to a site-specific recombination site, and when combined with Lenski et al. meet the limitations for a chloramphenicol antibiotic resistance gene and *E. coli* host cells, then this rejection must be maintained.

4. **Claims 35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fukushige et al. Wahl et al. (US 5,677,177), Lenski et al., and further in view of Griffiths et al. (US 5,962,255).**

This is a new ground of rejection necessitated by material changes to the claims. The teachings of Fukushige, Lenski and the '177 patent are incorporated and applied herein, consonant with the interpretations stated above. Additional embodiments are directed to the site-specific recombination site(s) as delimited to a lambdoid *att* site or mutants thereof. (i.e., claims 52-54, 58-64, 87-88, 90-91, 104-106).

The additional claims are essentially directed to the same nucleic acid molecules and host cells comprising the nucleic acid molecules, and only differ in the site-specific recombination system that is being claimed.

The limitation "lambdoid" is not specifically defined, but in general terms and in the context that it is recited in the relevant claims, the limitation is interpreted as delimiting *att* site(s) or mutants thereof that are associated with lambda (phage)-recognized *att* sites. The instant specification references to *att* sites obtained from or associated with lambda phage. (e.g., published version of this application; 2003/0064515, ¶ [0147]).

Fukushige and the '177 patent do not explicitly teach that the site-specific recombination site(s) can be lambdoid *att* sites. However, as far as site-specific recombination systems (i.e., recombinase proteins and binding sites) are concerned lambda phage *att* sites are routinely utilized in the relevant art interchangeably with other site-specific recombination systems (e.g.,Cre/*lox*, FLP/*Frt*, Int/*att*). Indeed, as Griffiths et al. state, "One of the most fully understood site-specific recombination systems is that used in integration and excision of bacteriophage lambda". (col. 19, l. 17).

Moreover, Griffiths et al. explicitly discuss both the *lox* and *att* systems in the context of site-specific recombination as interchangeable equivalents. (e.g., col. 19; especially ll. 19-48). As such, it would have been obvious to modify the expression vectors taught by Fukushige or the '177 patent, as utilized in host cells. One would have been motivated to make such a modification to obtain the benefit of extending the range of site-specific recombination systems (recombinases and their cognate substrate/recognition sites).

Furthermore, given the level of skill at the time of invention, there would have been a reasonable expectation of success to substitute one site-specific recombination system, as taught by Fukushige or the '177 patent, with the Int/*att* system as discussed by Griffiths et al.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DAVID GUZO
PRIMARY EXAMINER